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13. ABSTRACT (Maximum 200 words) Acute Mountain Sickness (AMS) is a multi-system disorder that is characterized by headache, anorexia, nausea, vomiting, insomnia, lassitude, and malaise. The syndrome is common in unacclimatized low altitude residents who rapidly ascend to terrestrial elevations exceeding 2,500 m. AMS may be a manifestation of hypoxia-induced cerebral edema resulting, in part, from increased capillary permeability. Hypothesis: We hypothesized that cysteinyl leukotrienes (CysLTs) may be involved in the pathogenesis of AMS, as these compounds are known to increase endothelial permeability. Methods: To test this hypothesis, we orally administered a CysLTs type-1 receptor antagonist (montelukast) to 11 subjects prior to and during exposure to high altitude (4300 m) in a hypobaric chamber in a randomized, placebo-controlled, crossover design. We measured the resulting prevalence and/or severity of AMS, plasma CysLTs levels and urinary CysLTE4, and associated physiological responses. Results: At 12 hr exposure, AMS prevalence and symptom severity was lower ( $p=0.002$ ) during montelukast administration compared to placebo, but not different at 22 hr exposure. Plasma CysLTs and urinary LTE4 levels were not significantly elevated at 22 hr exposure, nor did these CysLTs levels correlate with AMS severity. Compared to placebo, montelukast administration was not associated with any significant differences in physiologic measures at sea level or high altitude. Conclusions: These results do not support a role for the CysLTs mediating the early development of AMS through the CysLT-1 receptor.				
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# Cysteinyl Leukotriene Blockade Does Not Prevent Acute Mountain Sickness

STEPHEN R. MUZA, DAVID KAMINSKY, CHARLES S. FULCO,  
LOUIS E. BANDERET, AND ALLEN CYMERMAN

MUZA SR, KAMINSKY D, FULCO CS, BANDERET LE, CYMERMAN A. Cysteinyl leukotriene blockade does not prevent acute mountain sickness. *Aviat Space Environ Med* 2004; 75:413-9.

**Background:** Acute Mountain Sickness (AMS) is a multi-system disorder that is characterized by headache, anorexia, nausea, vomiting, insomnia, lassitude, and malaise. The syndrome is common in unacclimatized low altitude residents who rapidly ascend to terrestrial elevations exceeding 2,500 m. AMS may be a manifestation of hypoxia-induced cerebral edema resulting, in part, from increased capillary permeability. **Hypothesis:** We hypothesized that cysteinyl leukotrienes (CysLTs) may be involved in the pathogenesis of AMS, as these compounds are known to increase endothelial permeability. **Methods:** To test this hypothesis, we orally administered a CysLTs type-1 receptor antagonist (montelukast) to 11 subjects prior to and during exposure to high altitude (4,300 m) in a hypobaric chamber in a randomized, placebo-controlled, crossover design. We measured the resulting prevalence and/or severity of AMS, plasma CysLTs levels and urinary CysLTE4, and associated physiological responses. **Results:** At 12 h exposure, AMS prevalence and symptom severity was lower ( $p = 0.002$ ) during montelukast administration compared with placebo, but not different at 22 h exposure. Plasma CysLTs and urinary LTE4 levels were not significantly elevated at 22 h exposure, nor did these CysLTs levels correlate with AMS severity. Compared with placebo, montelukast administration was not associated with any significant differences in physiologic measures at sea level or high altitude. **Conclusions:** These results do not support a role for the CysLTs mediating the early development of AMS through the CysLT-1 receptor.

**Keywords:** high altitude illness, leukotrienes, montelukast, hypoxia.

**A**CUTE MOUNTAIN sickness (AMS) is a syndrome that is characterized by headache, anorexia, nausea, vomiting, insomnia, lassitude, and malaise. There is individual variation in susceptibility to the syndrome; however, the hypoxia-induced symptoms are most common in unacclimatized low-altitude residents who rapidly ascend to terrestrial elevations exceeding 2,500 m (10). In addition, the development of AMS appears to be promoted by engaging in physical activities at high altitude (7). The symptoms of AMS commonly appear within 4 to 24 h of exposure, and usually resolve after several days as acclimatization to hypoxia is achieved. AMS is usually self-limited, but may progress into high altitude cerebral edema (HACE) or high altitude pulmonary edema (HAPE), both of which are potentially life threatening.

Although there has been much speculation about the cause of AMS symptoms, little definitive information exists. The most widely accepted hypothesis is that the symptoms are a manifestation of a hypoxia-induced, subclinical cerebral edema that causes swelling of the

brain (11,15,29,30). In total, these studies point toward disruption of cerebral tissue fluid distribution as the likely cause of AMS. Increased cerebral extracellular fluid volume may result from vasogenic edema caused by increasing capillary pressure and/or capillary permeability. A number of observations suggest that inflammation may be an important factor in the pathogenesis of AMS. In support of this concept is the observation that the synthetic corticosteroid dexamethasone is effective in the prophylaxis and treatment of AMS (4,9,16,17,21). Dexamethasone blocks the formation of free arachidonic acid through an indirect effect on phospholipase A2 (31), leading in turn to decreased levels of both prostaglandins and leukotrienes. Naproxen, a known inhibitor of cyclooxygenase (prostaglandin synthesis) has no beneficial effect on AMS (20). This implies that products of the lipoxigenase pathway (primarily leukotrienes) may be responsible for causing the symptoms of AMS.

Patients with diseases that involve inflammation, such as asthma, have elevated levels of cysteinyl leukotriene E4 (LTE4) in their urine (2). LTE4 is the metabolite of the more potent cysteinyl leukotrienes C4 and D4 (2). An elevated urinary LTE4 level may in fact be a marker of generalized inflammation. It is reasonable to consider that leukotrienes may be involved in the pathogenesis of AMS because these compounds are known to increase endothelial permeability (2).

Several field studies have reported increased presence of leukotrienes concomitant with the development of AMS and HAPE. Richalet et al. (22) reported that serum levels of leukotriene B4 (LTB4), LTC4 (which is metabolized to LTE4, then excreted in the urine), and

From the Thermal and Mountain Medicine Division, U.S. Army Research Institute of Environmental Medicine, Natick, MA (S. R. Muza, C. S. Fulco, L. E. Banderet, A. Cymerman); and Pulmonary Disease and Critical Care Medicine, University of Vermont College of Medicine, Burlington, VT (D. Kaminsky).

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Address reprint requests to: Stephen R. Muza, Research Physiologist, Thermal and Mountain Medicine Division, U.S. Army Research Institute of Environmental Medicine, Natick, MA 01760-5007; Stephen.muza@us.army.mil.

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prostaglandin E2 increased in humans who rapidly ascended and resided at 4,350 m, generally peaking within 24 to 48 h after arrival. Their data also suggested a relationship between the levels of these mediators and AMS symptoms. Subsequently, we found that urinary LTE4 levels increased after about 12 h residence at 4,300 m (23). Furthermore, the data suggested a correlation between urinary LTE4 levels and AMS symptoms. Studies examining the bronchoalveolar lavage of victims of HAPE have shown fluid that is rich in neutrophils and proteins (28). Elevated levels of LTB4 and complement have also been found (27). In addition, many authors have described persistent pulmonary hypertension and infiltrates despite resolution of hypoxemia. This observation implies that an ongoing inflammatory process in the lungs is still operative. Indeed, we found that urinary LTE4 levels were elevated in 38 HAPE subjects compared with 10 control subjects present at the same altitude in Summit County, CO (14). On the other hand, a recent study performed in a hypobaric chamber reported no increase in urinary LTE4 during 20 h exposure to 4,000 m (1).

To test the hypothesis that the cysteinyl leukotrienes (LTC4, LTD4) are involved in mediating the development of AMS, we administered montelukast, a specific cysteinyl leukotriene (CysLTs) type-1 receptor blocker, in a randomized, double-blinded, placebo-controlled crossover trial at a simulated altitude of 4,300 m. The specific objectives of this study were to assess the effects of CysLTs type-1 receptor blockade in sea level residents during 24 h of exposure to 4,300 m on the following: 1) the presence or absence and severity of signs and symptoms of AMS; 2) specific ventilatory, cardiovascular, body fluid, and other physiologic parameters indicative of the early acclimatization process; and 3) markers of inflammation and hypoxic stress.

## METHODS

### Subjects

There were 12 volunteers who enrolled in this study. All gave written and verbal acknowledgment of their informed consent according to the procedures approved in advance by the Institutional Review Boards of the U.S. Army and the University of Vermont. Each was a lifelong low-altitude resident and had no exposure to altitudes greater than 1,000 m for at least 6 mo immediately preceding the study. All volunteers received medical examinations, and none were found to have any condition that would warrant exclusion from the study. All were U.S. Army personnel who participated in regular physical training and were of average fitness. There were 11 subjects (9 male, 2 female) who completed all elements of the protocol. The 11 subjects had a mean ( $\pm$  SD) age, height, and body weight of  $24 \pm 4$  yr,  $175 \pm 8$  cm, and  $81 \pm 13$  kg.

### Protocol

The study design was a randomized, double-blinded, placebo-controlled crossover trial. The test subjects were exposed sequentially to sea level and high altitude for testing purposes in the USARIEM hypobaric cham-

ber facility in Natick, MA, on two occasions (test phases); once while on the leukotriene antagonist and once on the placebo. The sea-level exposure was 24 h in length and immediately preceded the altitude exposure. Sea-level exposure was at ambient barometric pressure (approximately 760 mmHg) in the hypobaric chamber. Testing at sea-level pressure in the hypobaric chamber functioned as the control condition for subsequent altitude (hypobaric) testing. Following completion of the sea-level testing, the chamber containing the subjects was decompressed at a rate of  $45 \text{ mmHg} \cdot \text{min}^{-1}$  to a pressure of 446 mmHg, which is approximately equivalent to a terrestrial altitude of 4,300 m (14,110 ft). The subjects remained at that altitude continuously for 24 h until the completion of testing. Following completion of the altitude testing, the chamber was recompressed to ambient barometric pressure.

The temperature and relative humidity in the chamber was maintained at  $21 \pm 2^\circ\text{C}$  and  $45 \pm 5\%$ , respectively, for all testing. Subjects were allowed to participate in sedentary activities (reading, TV viewing) when not involved in actual testing during each test phase. For logistical purposes, subjects were exposed to sea-level and altitude conditions in groups of five to six individuals.

For each test volunteer the study schedule required about 6 wk, and included a preliminary phase, the two test phases, and intervening recovery periods. During the preliminary phase (about 3 d), subjects received required hypobaric chamber orientation and safety training, were familiarized with the test procedures, and had a short (approximately 6 h) exposure in the hypobaric chamber. The purpose of this short high-altitude exposure was to familiarize the subjects with the perceptual cues associated with the chamber environment and perceived symptoms related to the hypobaric hypoxia and exercise stresses. We expected that this familiarization would reduce the "novelty factor" influence on the reporting of subjective symptoms during the subsequent two test phase high-altitude exposures. Following the preliminary phase, the subjects had at least a 7-d recovery period to avoid any carryover effects from the first altitude exposure into the first test phase. The two test phases were each 2 d in length and were separated by a 12–14 d recovery period to avoid carryover effects.

Pharmacologic blockade of CysLTs type-1 (CysLT-1) receptors was produced by ingestion of montelukast sodium. Montelukast (Singulair®, Merck & Co., Inc., West Point, PA) is a CysLT-1 receptor antagonist that is approved by the U.S. Food and Drug Administration for clinical use for the prophylaxis and chronic treatment of asthma (12). Montelukast is an orally active compound that binds with high affinity and selectivity to CysLT-1 receptors. Following oral administration, it is rapidly absorbed and reaches peak plasma concentration in 3–4 h. The mean plasma half-life of montelukast ranges between 2.7–5.5 h in normal healthy adults. Montelukast is more than 99% bound to plasma proteins and has minimal distribution across the blood-brain barrier. Although doses up to  $200 \text{ mg} \cdot \text{d}^{-1}$  have been tested, no clinical benefit has been observed at

doses above 10 mg once daily. The first dose of montelukast (10 mg film-coated tablet) was given at 08:00 at the beginning of a test phase and the second 10-mg dose was given about 24 h later just prior to decompressing the chamber to simulated altitude. During the placebo trial, an identical-appearing tablet containing lactose was ingested on the same schedule during its corresponding test phase.

To minimize the effects of diet on gastrointestinal symptoms and loss of appetite associated with AMS, during both test phases each volunteer was required to consume a preselected diet and maintain hydration by drinking a recommended amount of fluid each day based on body weight. The diet consisted of commercially prepared food items and non-prepared items. Each volunteer selected his or her choices for each meal from a menu prior to the first test phase. They were given similar meals during the second test phase.

Since military duties normally require physical work and development of AMS is promoted by physical activity at high altitude, each volunteer performed a circuit of resistive and aerobic exercises for about 2 h, including rest breaks, during the high altitude exposures. Resistive exercise consisted of bench press and arm curl exercises performed over 20 min in 5 sets (8–10 repetitions of a 12-repetition max workload). In between each set, the volunteer rested approximately 3 min. The aerobic exercise was a 20-min submaximal, steady-state exercise bout on a bicycle ergometer at 70% of the subject's predicted heart rate maximum. Heart rate (HR) was measured by three-lead ECG, and  $S_{aO_2}$  was monitored by finger pulse oximetry (Nellcor N-200, Nellcor, Pleasanton, CA).

#### Measurements

The incidence and severity of AMS was determined from information gathered using the Environmental Symptoms Questionnaire (ESQ), and the Lake Louise AMS Scoring System (LL AMS). The ESQ is a self-reported, 68-question inventory used to document symptoms induced by altitude and other stressful environments (25). A weighted average of scores from "cerebral" symptoms (headache, lightheaded, dizzy, etc.) designated ESQ-C were calculated. ESQ-C scores  $\geq 0.7$  are defined as indicating the presence of AMS. The LL AMS consists of a five-question self-reported assessment of AMS symptoms and a three-question objective assessment of clinical signs (24). It appears to successfully detect AMS and correlates with ESQ scores (26). The total LL AMS score consisting of the sum of the self-assessment question score and the clinical-assessment score was calculated for each subject post hoc. A total LL AMS score  $\geq 3$  was defined as indicating the presence of AMS. The ESQ and LL AMS were administered twice during the preliminary phase to familiarize the test subjects with the procedures. The ESQ was administered at 1, 2, 4, 10, 12, 20, and 22 h into each 24-h long sea-level and high-altitude exposure. The LL AMS was administered at 12 and 20 h into each 24-h long sea-level and high-altitude exposure. Coincident with the administration of the ESQ, resting  $S_{aO_2}$  and HR were measured.

Resting ventilation measurements were made in each test phase once at sea level and again at high altitude in the morning prior to breakfast. All ventilatory tests were performed with the subjects resting in a seated position. The volunteer breathed through a low-resistance respiratory valve and breathing circuit connected to a computer-controlled, breath-by-breath metabolic measurement system (Vmax229, SensorMedics Corp, Yorba Linda, CA). Resting ventilation tests measured breath-by-breath: minute ventilation ( $V_E$ ), oxygen uptake ( $VO_2$ ), carbon dioxide elimination ( $VCO_2$ ), and partial pressure end-tidal oxygen and carbon dioxide ( $P_{eO_2}$  and  $P_{eCO_2}$ ). Simultaneously,  $S_{aO_2}$  and pulse rate were measured by finger pulse oximetry (Nellcor N-200, Nellcor, Pleasanton, CA). Resting ventilation tests were about 20 min in duration. Resting ventilatory parameters were obtained and mean values calculated from the last 8–10 min of the session. Following the resting ventilatory studies, flow-volume loops were obtained to assess possible altitude-induced changes in forced vital capacity (FVC) and forced expired volume in the first second (FEV<sub>1</sub>). The procedure was performed three to five times until reproducibility criteria (8) were achieved.

During the two test phases, venous blood samples were obtained after arousal on the mornings of day 2 (sea level) and day 3 (22 h altitude exposure). These morning samples of whole blood were immediately analyzed for hemoglobin (Hb) and hematocrit (Hct). The remaining blood was processed and stored for later analysis of eicosanoids. Body fluid status was assessed by measuring 24-h urinary volume, daily body weight, and urinary and plasma osmolality ( $U_{osm}$ ,  $V_{osm}$ ). We calculated 24-hr urine volume from measurement of separate 12-h urine collections. Aliquots of the 12-h urine collections were taken for analysis of creatinine ( $U_{creat}$ ) and  $U_{osm}$ . Urinary LTE4 concentrations were determined by reverse-phase HPLC and ELISA in aliquots of the second 12-h urine collections at sea level and high altitude. Plasma concentrations of LTC4, LTD4, LTE4, and LTB4 were measured by microtiter plate ELISA (Core Endocrine Laboratory, Hershey, PA).

#### Statistical Analysis

First, two-way (CysLT-1 receptor blockade and altitude exposure duration) analysis of variance with repeated measures in both factors was used to analyze the data. Significant effects or interactions identified by the ANOVA were examined using a post hoc Bonferroni *t*-test for multiple comparisons. Data that deviated significantly from normality or failed to meet the qualifying assumptions of analysis of variance were analyzed using appropriate non-parametric techniques (i.e., ANOVA on ranks, or Mann-Whitney rank sum test, etc) (6). Second, the subjects were then divided into two groups depending on whether they developed or did not develop AMS (AMS+ or AMS-). High altitude measurements of the AMS+ and AMS- groups within each drug treatment were compared using the Student's *t*-test, or if the data deviated significantly from normality or failed to meet the qualifying assumptions of analysis of variance, the data were analyzed using

TABLE I. AMS SCORES AND PHYSIOLOGICAL PARAMETERS AT HIGH ALTITUDE IN THE PLACEBO AND MONTELUKAST TRIALS.

Variable	Placebo Trial	Montelukast Trial
ESQ-C Score (12 h)	0.653 ± 0.751	0.378 ± 0.348
ESQ-C Score (22 h)	0.915 ± 0.981	0.778 ± 0.647
LL AMS Score (12 h)	4.5 ± 3.7	1.8 ± 2.0*
LL AMS Score (22 h)	7.1 ± 4.2	5.7 ± 5.0
SaO <sub>2</sub> (%)	82 ± 5	82 ± 3
P <sub>et</sub> CO <sub>2</sub> (mmHg)	31.7 ± 4.0	32.1 ± 2.7
Hb (g · dl <sup>-1</sup> )	15.2 ± 1.3	15.2 ± 1.07
SL uLTE <sub>4</sub> (pg · mg <sup>-1</sup> )	80.5 ± 36.5	79.4 ± 38.5
HA uLTE <sub>4</sub> (pg · mg <sup>-1</sup> )	90.2 ± 39.7	101.8 ± 48.0
24-hr Uvol (L)	2.6 ± 1.6	3.0 ± 1.9
ΔBW (kg)	0.06 ± 0.59	0.07 ± 0.95

SL: sea level; HA: high altitude (4,300 m); u: urine; n = 11.

\*p &lt; 0.05 montelukast vs. placebo.

the Mann-Whitney Rank Sum Test. Potential relationships between measured parameters were tested using the Pearson Product Moment Correlation. Statistical significance was accepted at  $p \leq 0.05$ . Values are presented as mean ± SD.

## RESULTS

During the placebo trial, 7 of the 11 subjects developed AMS assessed by ESQ-C scores while 9 developed AMS according to the LL AMS score. During the montelukast trial, by both the ESQ-C and LL AMS scores, AMS developed in the same 7 subjects in whom it was observed during the placebo trial. A significant interaction between altitude exposure duration and drug ( $p = 0.030$ ) was observed in the LL AMS scores, but not the ESQ-C AMS scores ( $p = 0.343$ ). As measured by LL, the AMS scores were significantly less ( $p = 0.002$ ) at 12 h of altitude exposure in the montelukast compared with the placebo trials (Table I). However, by 22 h exposure, AMS severity by the LL AMS score was not different ( $p = 0.098$ ) between drug treatments.

There was a wide range in interindividual AMS severity during both trials. This is illustrated in Fig. 1, which plots the cumulative AMS symptom scores for each individual in both trials. Visual inspection of these plots shows that individual subject symptom scores were roughly comparable between trials. There is a suggestion that the subjects with the higher AMS symptom severity in the placebo trial experienced the greatest decrease in symptom severity in the montelukast trial (data points deviate rightward from the line of identity at the higher placebo AMS scores); however, statistical analysis did not support a significant effect of montelukast on AMS severity in these subjects. Furthermore, none of the physiological parameters measured at sea level or during the altitude exposure were significantly different between the placebo and montelukast trials (Table I).

To determine if physiological differences existed between subjects who were and were not susceptible to AMS, within each trial, the subjects were partitioned into those who developed AMS (AMS+) and those who did not (AMS-). These data are presented in Table II. In the placebo trial, resting SaO<sub>2</sub> was significantly lower

in the AMS+ group compared with the AMS- group. This SaO<sub>2</sub> difference was not present in the montelukast trial, nor was any other significant physiological differences observed between the AMS+ and AMS- subjects.

Interindividual levels of urinary LTE<sub>4</sub> were widely dispersed at sea level and high altitude during both trials. As shown in Fig. 2, there was a strong correlation ( $r = 0.91$ ,  $p < 0.001$ ) between individual sea level urinary LTE<sub>4</sub> and high altitude urinary LTE<sub>4</sub> levels. However, urinary LTE<sub>4</sub> levels following 12–24 h at high altitude were not significantly different from sea level values (Tables I, II) in either trial. AMS symptom severity scores by either ESQ-C or LL AMS were not correlated with either the pre-ascent sea level or high altitude urinary LTE<sub>4</sub> levels in either trial. Plasma concentrations of the CysLTs (LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>) and LTB<sub>4</sub> were measured during the placebo trial only (Table II). Similar to the urinary LTE<sub>4</sub> data, strong correlations were observed between the individual sea level and high-altitude levels. Likewise, plasma CysLTs and LTB<sub>4</sub> concentrations were not statistically different between sea level and 22 h high-altitude exposure, and no correlation was observed between individual plasma levels of either LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>, or LTB<sub>4</sub> and AMS symptoms severity scores.

## DISCUSSION

This study tested the hypothesis that the CysLTs (LTC<sub>4</sub>, LTD<sub>4</sub>) are involved in mediating the development of AMS. To test this hypothesis, we administered montelukast, a specific CysLT-1 receptor blocker, in a randomized, double-blinded, placebo-controlled crossover trial at 4,300 m altitude. Although AMS prevalence

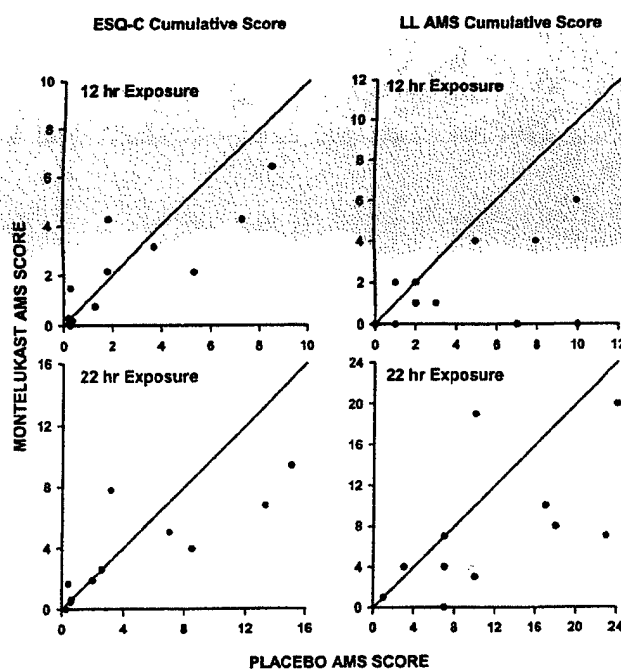


Fig. 1. Scatter plots showing the relationship between individual AMS severity scores during placebo and montelukast trials. The line of identity is plotted for reference.

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TABLE II. AMS SCORES AND PHYSIOLOGICAL PARAMETERS AT HIGH ALTITUDE SEGREGATED BY AMS SUSCEPTIBILITY (ESQ-C SCORE) IN THE PLACEBO AND MONTELUKAST TRIALS.

Variable	Placebo		Montelukast	
	AMS+	AMS-	AMS+	AMS-
ESQ-C (#Ss)	7	4	7	4
ESQ-C Score	1.05 ± 0.75*	0.07 ± 0.02	0.76 ± 0.39*	0.10 ± 0.10
SpO <sub>2</sub> (%)	80 ± 4*	85 ± 3	82 ± 3	83 ± 5
P <sub>et</sub> CO <sub>2</sub> (mmHg)	31.4 ± 4.3	32.4 ± 3.9	31.6 ± 2.5	33.1 ± 3.0
Hb (g · dl <sup>-1</sup> )	15.6 ± 0.9	14.7 ± 1.8	15.5 ± 0.77	14.6 ± 1.4
SL uLTE <sub>4</sub> (pg · mg <sup>-1</sup> )	86.0 ± 42.7	71.0 ± 24.3	86.4 ± 40.9	67.0 ± 35.8
HA uLTE <sub>4</sub> (pg · mg <sup>-1</sup> )	96.0 ± 44.6	80.0 ± 32.3	104.4 ± 48.2	97.0 ± 54.7
SL pLTC <sub>4</sub> D <sub>4</sub> E <sub>4</sub> (pg · ml <sup>-1</sup> )	152.0 ± 88.7	124.5 ± 49.4		
HA pLTC <sub>4</sub> D <sub>4</sub> E <sub>4</sub> (pg · ml <sup>-1</sup> )	135.3 ± 55.5	131.0 ± 58.5		
SL pLTB <sub>4</sub> (pg · ml <sup>-1</sup> )	582.7 ± 243.4	540.5 ± 159.3		
HA pLTB <sub>4</sub> (pg · ml <sup>-1</sup> )	556.3 ± 50.7	437.0 ± 143.3		
24-hr Uvol (L)	2.4 ± 1.4	2.8 ± 1.9	3.0 ± 2.1	2.9 ± 1.9
ΔBW (kg)	-0.04 ± 0.22	0.25 ± 0.99	-0.20 ± 0.70	0.55 ± 1.24

SL: sea level; HA: high altitude (4,300 m); u: urine; p: plasma;

\*p < 0.05 AMS+ vs. AMS-.

and symptom severity by LL AMS was lower during montelukast administration compared with placebo during the first 12 h exposure, the weight of evidence does not support our hypothesis. Neither the urine or plasma levels of CysLTs were significantly elevated after 20 h exposure, nor did CysLTs levels correlate with AMS severity, suggesting that LTC<sub>4</sub> or LTD<sub>4</sub> were not mediating the development of AMS. Thus, these results do not support a role for the CysLTs mediating the early development of AMS through the CysLT-1 receptor.

All studies of AMS are beset by two limitations that must be considered in the interpretation of the results. The first is that susceptibility to AMS is not uniform among all subjects and the second is that the assessment of AMS is dependent on each volunteer's subjective

reporting of their symptoms. The ideal test of a pharmacological intervention to prevent or reduce symptoms of AMS would only use a subject population with known, uniform susceptibility to AMS. However, lacking that population, under the ascent conditions used in this study, between 60–75% of the subjects were expected to experience some degree of AMS (13,18), and according to the results they did. Thus, only the subjects who reported experiencing AMS during the placebo trial (7 by ESQ-C, 9 by LL AMS) are useful in assessing whether the pharmacological intervention is effective. However, even among these AMS-susceptible subjects, the AMS severity varied from very mild to severe. Consequently, the reduction in subject number and large variance in the symptom severity decrease the statistical power to detect potentially clinically important effects of the pharmacological intervention.

Two instruments were used to assess AMS severity, the ESQ-C and LL AMS scores. Both instruments are questionnaires that ask subjects to assign a categorical rating to symptoms associated with AMS. The LL AMS identified more subjects with AMS than the ESQ, but the scores between the two assessments were highly correlated ( $r = 0.78$  to  $0.98$ ). Thus, the threshold for assigning a diagnosis of AMS appears to be lower using the LL AMS compared with the ESQ-C AMS scores. Consequently, due to the larger number of AMS-susceptible subjects per LL AMS scores, a statistically significant reduction in LL AMS symptom severity was observed in the montelukast trial compared with the placebo trial after 12 h altitude exposure. Although this reduction in early AMS severity would appear to support our hypothesis, the fact that all subjects that developed AMS on placebo subsequently developed AMS on montelukast and that plasma leukotriene levels did not increase with high altitude exposure does not support our hypothesis that blocking the action of CysLT-1 receptors decreases the prevalence and severity of early AMS.

We did not observe an increase in either plasma or urinary CysLTs levels following 20–24 h of high altitude exposure, which we would have expected if in-

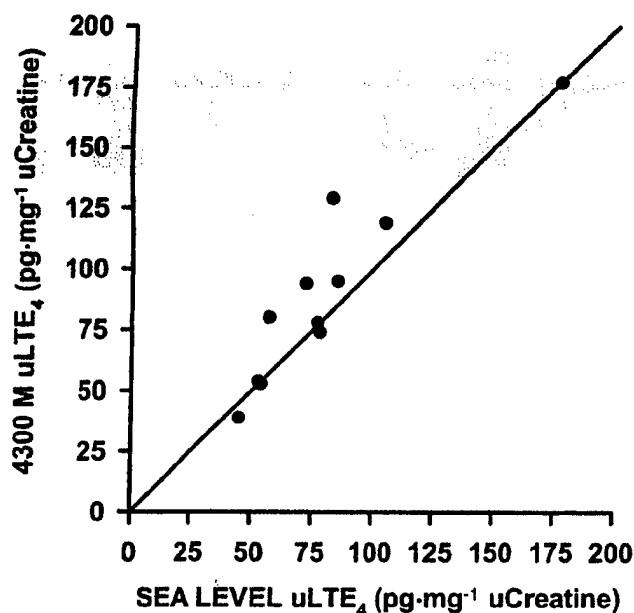


Fig. 2. Scatter plot showing the relationship between individual urinary LTE<sub>4</sub> levels at sea level and after 24 h at 4,300 m. The line of identity is plotted for reference.



creased production of CysLTs were involved in the pathogenesis of AMS. Previously, we reported an increase in urinary LTE4 following overnight residence at 4,300 m, and a positive correlation between urinary LTE4 levels and AMS severity (23). In addition, increases in urinary LTE4 were reported during an expedition to altitudes ranging between 3,000–5,025 m (32). The current study did not find any increase in urinary LTE4, nor was any increase found in another recent study that measured urinary LTE4 following 20 h exposure to 4,000 m in a hypobaric chamber (1). A review of these reports reveals that the studies demonstrating increases in urinary LTE4 used only first morning voids for their urine collections, and that the subjects had been exposed to altitudes above 2,000 m for more than 24 h. The present study and that by Bartsch and colleagues (1) reporting no increase in urinary LTE4, collected 12- or 24-h urine samples, respectively, from which the aliquot for urinary LTE4 assay was taken. Thus, it is possible that the rise in urinary LTE4 was diluted by the longer duration urine collection period. However, we did not observe a rise in the plasma concentration of CysLTs assayed in a venous blood sample drawn following 20 h of altitude exposure. Furthermore, the plasma levels of CysLTs were positively correlated with the urinary LTE4 levels ( $r = 0.62$ ,  $p = 0.0034$ ). Thus, the plasma CysLTs data suggests that the measured urinary LTE4 levels are valid indices of the plasma levels. This leaves the possibility that the elevated urinary LTE4 levels observed in the field studies are associated with longer duration exposure to hypoxia and/or coexisting factors such as prolonged physical exertion common to trekking or mountaineering activities.

The lack of an increase in CysLTs levels in the plasma during the first 20 h of altitude exposure suggests that CysLTs are not primary mediators of AMS development. Previous work suggests that another leukotriene, LTB<sub>4</sub>, may be responsible for mediating the development of AMS. Richalet et al. (22) reported that the increase in plasma LTB<sub>4</sub> paralleled the development of AMS. In addition, LTB<sub>4</sub> is a potent mediator of capillary permeability (3,5,19). Since montelukast does not affect LTB<sub>4</sub> production or activity, we cannot discount the possibility that LTB<sub>4</sub> mediates development of AMS either alone, or in conjunction with LTC<sub>4</sub>. However, we observed no increase in plasma LTB<sub>4</sub> levels following 20 h exposure to high altitude (Table II), nor were individual plasma LTB<sub>4</sub> levels related to AMS symptom scores. This suggests that LTB<sub>4</sub> as well as the CysLTs do not play a principal role in the early development of AMS.

In summary, we administered montelukast, a specific CysLT-1 receptor blocker, in a randomized, double-blinded, placebo-controlled crossover trial at 4,300 m altitude to determine if CysLTs are involved in the development of AMS. Compared with placebo, montelukast administration did not substantially decrease AMS prevalence or symptom severity during 22-h altitude exposure. Furthermore, we observed no increase in plasma or urinary levels of the CysLTs or LTB<sub>4</sub> concomitant with the development of AMS. These re-

sults suggest that leukotrienes LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>, and LTB<sub>4</sub> are not the principal mediators of the early development of AMS.

The views, opinions and/or findings in this publication are those of the authors, and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other documentation.

For the protection of human subjects, the investigators adhered to policies of applicable Federal Law CFR 46.

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